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GB 2225576 A EP 0184162 A2

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(71) Applicant
Fujisawa Pharmaceutical Co. Ltd

(Incorporated in Japan)

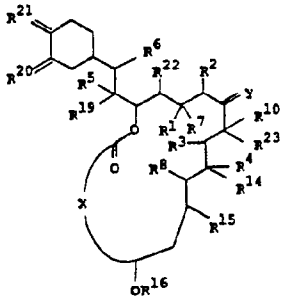
4-7 Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541, Japan

(72) Inventors
Chiyoshi Kasahara
Takehiko Ohkawa
Masashi Hashimoto

(74) Agent and/or Address for Service
Stevens, Hewlett and Perkins
5 Quality Court, Chancery Lane, London, WC2A 1HZ, United Kingdom

(54) Tricyclo compounds

(57) Compounds of the formula:

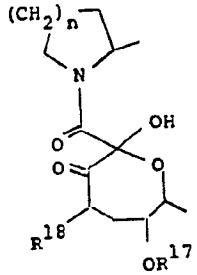


wherein each vicinal pair of substituents [R^1 and R^2], [R^3 and R^4], [R^5 and R^6] independently

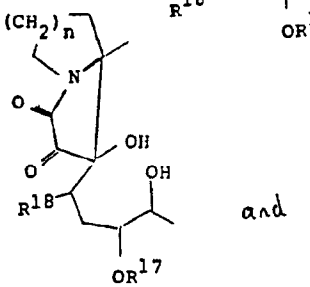
a) represent two vicinal hydrogen atoms, or
b) form a second bond between the vicinal carbon atoms to which they are attached;
in addition to its significance above, R^2 may represent an alkyl group;

Y represents O, (H,OH), (H, H), N-$NR^{11}R^{12}$ or N-OR^{13};

X represents a group of the formula:



or a group of the formula:



and

n is 1, 2 or 3, the remaining R groups being hydrogen atoms or various defined substituents which may in certain cases complete an additional ring, possess *immunosuppressive* and *antimicrobial activities*.

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TRICYCLO COMPOUNDS, A PROCESS FOR THEIR PRODUCTION AND A PHARMACEUTICAL COMPOSITION CONTAINING THE SAME

This invention relates to novel tricyclo compounds having pharmacological activities, to a process for their production and to a pharmaceutical composition containing the same.

More particularly, it relates to novel tricyclo compounds, which have pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof as a medicament.

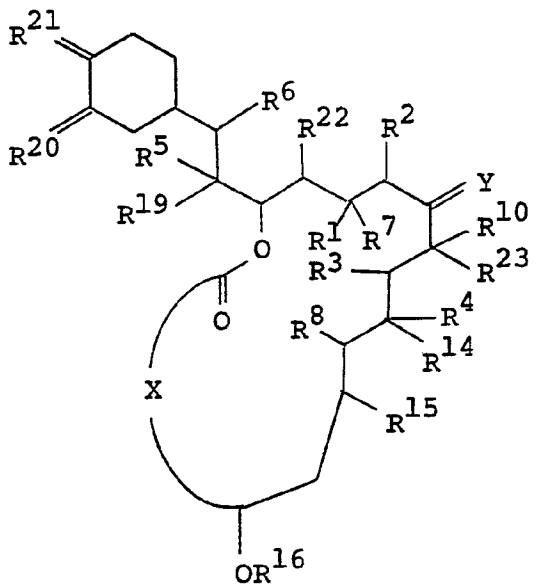
Accordingly, one object of this invention is to provide the novel tricyclo compounds, which are useful for treatment and prevention of resistance to transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like.

Another object of this invention is to provide a process for production of the tricyclo compounds by synthetic process.

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the tricyclo compounds.

Still further object of this invention is to provide a use of the tricyclo compounds as a medicament for treating and preventing resistance to transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like.

The new tricyclo compounds of this invention can be represented by the following general formula :



(I)

wherein each vicinal pair of substituents [R^1 and R^2], [R^3 and R^4], [R^5 and R^6] independently

a) represent two vicinal hydrogen atoms, or

b) form a second bond between the vicinal carbon atoms to which they are attached;

in addition to its significance above, R^2 may represent an alkyl group;

R^7 represents H, OH, protected hydroxy or O-alkyl, or in conjunction with R^1 it may represent =O;

R^8 represents H or OH;

R^{10} represents H, alkyl, alkyl substituted by one or more hydroxyl groups, alkenyl, alkenyl substituted by one or more hydroxyl groups, or alkyl substituted by =O;

Y represents O, (H,OH), (H,H), N-$NR^{11}R^{12}$ or N-OR^{13};

R^{11} and R^{12} independently represent H, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} independently represent H or alkyl;

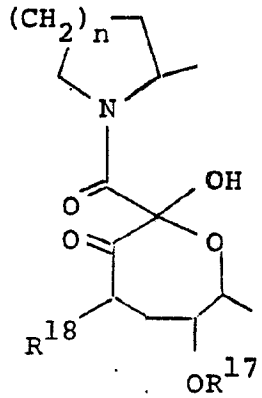
R^{20} and R^{21} independently represent O, or they may independently represent (R^{20}a,H) and (R^{21}a,H) respectively;

R^{20}a and R^{21}a independently represent OH, O-alkyl or $OCH_2OCH_2CH_2OCH_3$ or R^{21}a represents protected hydroxy;

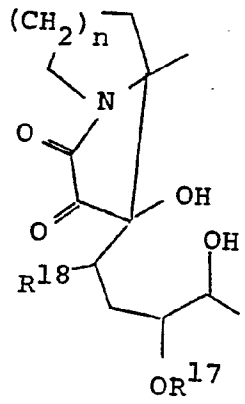
in addition, R^{20}a and R^{21}a may together represent an oxygen atom in an epoxide ring;

n is 1, 2 or 3;

X represents a group of the formula :



or a group of the formula :



in which R^{17} and R^{18} are each the same definitions as R^{13} and

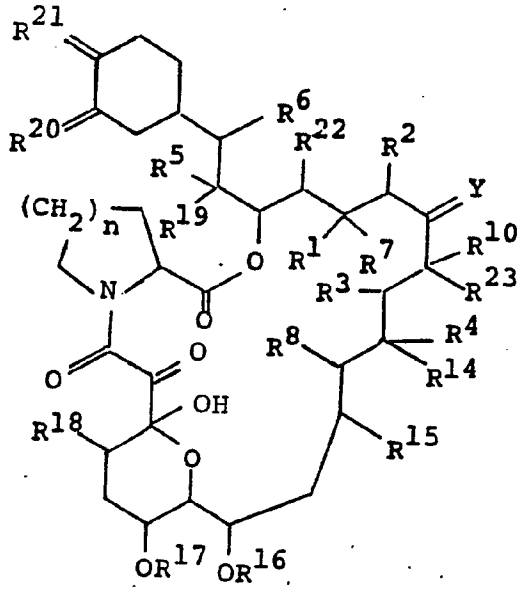
n is 1, 2 or 3;

in addition to their significances above, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a 5- or 6- membered N-, S- or O-containing, heterocyclic ring, which may be saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl, hydroxy, alkyl substituted by one or more hydroxyl groups, O-alkyl, benzyl and $-CH_2Se(C_6H_5)$;
and pharmaceutically acceptable derivatives thereof.

with respect to the tricyclo compounds (I) of this invention, it is to be understood that there may be one or more conformer(s) or stereoisomeric pairs such as optical and geometrical isomers due to asymmetric carbon atom(s) and double bond(s), and such isomers and also included within a scope of this invention.

According to this invention, the object tricyclo compounds (I) can be prepared by the following process.

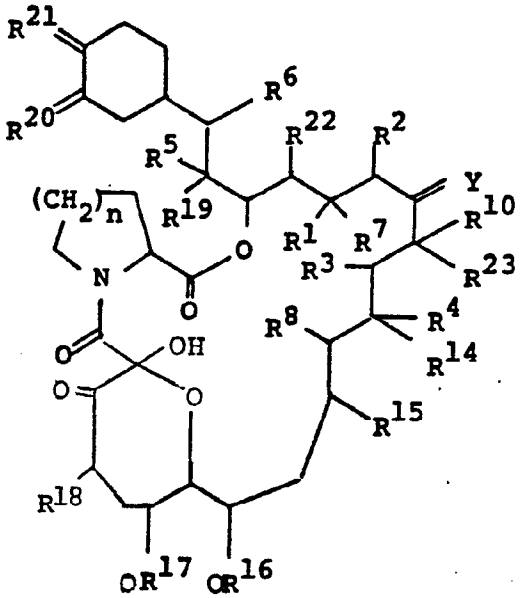
Process



(II)

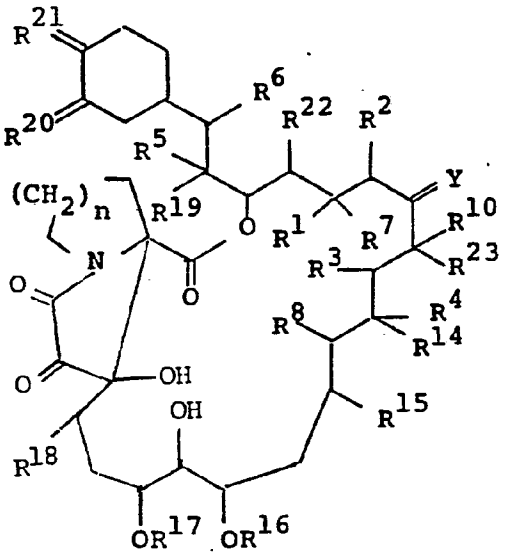
or a salt thereof

Rearrangement



(I-a)

or a salt thereof



(I-b)

or a salt thereof

wherein R^1 to R^8, R^{10}, R^{14} to R^{23}, Y and n are each as defined above.

Particulars of the above definitions and the preferred embodiments thereof are explained in detail as follows.

The term "lower" used in the specification is intended to mean 1 to 6 carbon atoms, unless otherwise indicated.

Suitable "alkyl" means straight or branched saturated aliphatic hydrocarbon residue and may include lower alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl, and the like.

Suitable "alkenyl" means straight or branched unsaturated aliphatic hydrocarbon residue having one double bond and may include lower alkenyl such as vinyl, propenyl, butenyl, methylpropenyl, pentenyl, hexenyl, and the like.

Suitable "aryl" may include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, and the like.

Suitable "protected hydroxy" may include 1-(lower alkylthio)(lower)alkyl, trisubstituted silyl and acyl as exemplified in European Patent Publication No. 0184162.

Suitable "5- or 6-membered N-, S- or O- containing heterocyclic ring" may include pyrrolyl, tetrahydrofuryl, and the like.

Preferred embodiments of the Symbols R^1 to R^8, R^{10}, R^{14} to R^{23}, Y and n are as follows.

R^1 and R^2 are each hydrogen or combined to form a second bond;

R^3 and R^4 are combined to form a second bond;

R^5 and R^6 are combined to form a second bond;

R^7 is hydrogen, hydroxy, O-lower alkyl such as methoxy or protected hydroxy;

R^8 is hydrogen;

R^{10} is methyl, ethyl, propyl or allyl;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are each methyl;

R^{20} is oxo or [R^{20}a,H], wherein R^{20}a is hydroxy or methoxy;

R^{21} is [R^{21}a,H], wherein R^{21}a is hydroxy or protected hydroxy;

R^{23} is hydrogen;

Y is oxo; and

n is 1 or 2.

Salts of the tricyclo compounds of the present invention include all pharmaceutically acceptable salts without limitation.

The process for production of tricyclo compounds (I) of this invention is explained in the following.

The compound (I-a) or a salt thereof and the compound (I-b) or a salt thereof can be prepared by subjecting the compound (II) or a salt thereof to rearrangement.

The reaction may be carried out in a conventional manner using base, and the like, which is explained in detail in the below example.

The reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, acetone, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, pyridine, benzene, N,N-dimethylformamide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually conducted under from cooling to heating.

The object tricyclo compounds (I) obtained according to the process as explained above can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, an the like.

PHARMACOLOGICAL ACTIVITIES OF THE TRICYCLO COMPOUNDS

The tricyclo compounds (I) possess pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, and therefore are useful for the treatment and prevention of the resistance by transplantation of organs or tissues such as heart, kidney, liver, medulla ossium, skin, cornea etc., graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple scleroiss, myasthenia gravis, type I diabetes, uveitis such as Behcet's disease, etc., vernal keratoconjunctivitis, infectious diseases caused by pathogenic microorganisms, and the like.

And further, the tricyclo compounds (I) are also

useful in the topical administration for the treatment and the prophylaxis of inflammatory and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses, such as, psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeis dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angoiedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus and Alopecia areata.

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the tricyclo compounds (I), as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, injections, ointments, liniments, eye drops lotion, gel, creme and any other form suitable for use. The carriers which can be used are water, glucose lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening, solubilizing an coloring agents and perfumes may be used. Particularly, as a solubilizing agent, there may be exemplified water-soluble cellulose polymer (i.e. hydroxypropyl methylcellulose, etc.), water-soluble glycol (i.e. propylene glycol, etc.), etc. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon

the process or condition of diseases.

For applying this composition to human, it is preferable to apply it by parenteral or enteral administration. While the dosage of therapeutically effective amount of the tricyclo compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg, of the active ingredient is generally given for treating diseases, and an average single dose of about 0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered.

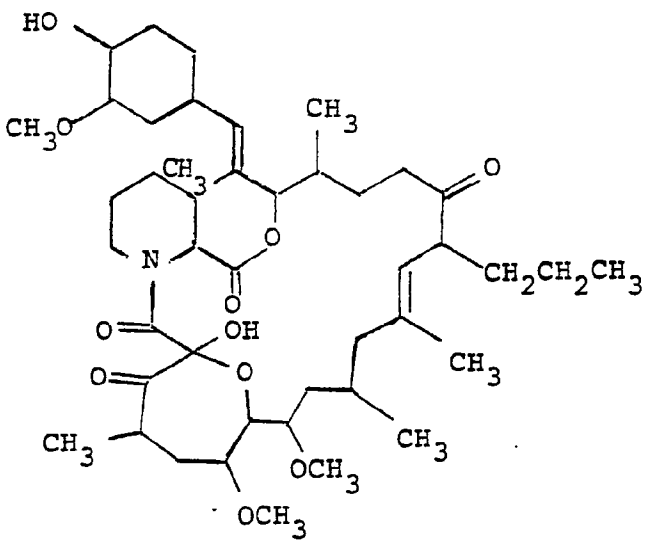
The following example is given for the purpose of illustrating the present invention.

Example 1

To a solution of 1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-17-propyl-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (300 mg) in tetrahydrofuran (9 ml) was added p-toluenesulfonamide sodium salt (81 mg) at room temperature. Then to this suspension was added dimethylsulfoxide (2 ml) and stirred for 4 hours. The reaction mixture was diluted with diethyl ether and washed with water and brine, and dried over magnesium sulfate. The solution was concentrated in vacuo, and the residue was purified by silica gel column chromatography (ethyl acetate-hexane 3:1, V/V) to give 1-hydroxy-11-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-22,24-dimethoxy-12,18,20,26-tetramethyl-10,28-dioxa-16-propyl-3-azatricyclo[21.4.1.$0^{3,8}$]octacos-17-ene-2,9,15,27-

tetraone, which can be represented by the following formula (A), (55 mg) and 16,20-dihydroxy-4-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-15,17-dimethoxy-5,11,13,19-tetramethyl-3-oxa-9-propyl-23-azatricyclo[18.7.0.$0^{1,23}$]heptacos-10-ene-2,8,21,22-tetraone, which can be represented by the following formula (B), (25 mg).

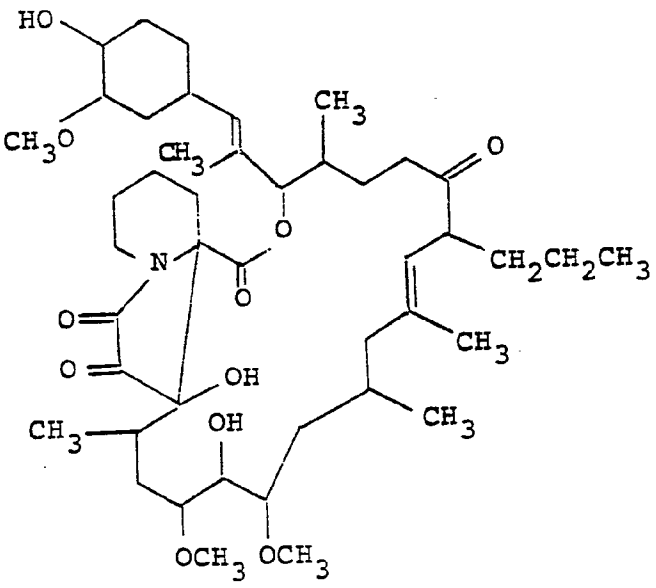
(A)



FAB MS : m/z 812 (M + Na)

^{13}C-NMR ($CDCl_3$, δ) : 73.3, 73.4, 74.8, 79.6, 79.8, 84.0, 96.6, 124.1, 131.0, 131.4, 137.6, 169.7, 170.0, 210.6, 211.2,

(B)

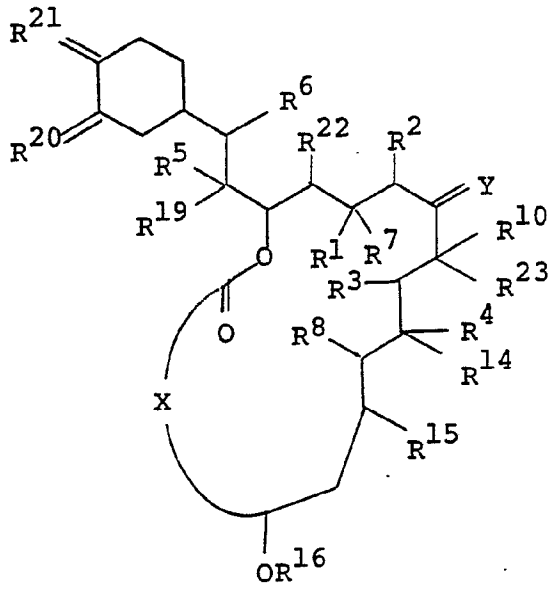


FAB MS : m/z 812 (M + Na)

^{13}C-NMR ($CDCl_3$, δ) : 72.2, 73.3, 76.6, 78.1, 78.9, 83.9, 85.9, 124.6, 131.1, 134.5, 138.8, 164.3, 169.9, 202.5, 210.6.

What we claim is :

1. A compound of the formula :



wherein each vicinal pair of substituents [R^1 and R^2], [R^3 and R^4], [R^5 and R^6] independently

a) represent two vicinal hydrogen atoms, or

b) form a second bond between the vicinal carbon atoms to which they are attached;

in addition to its significance above, R^2 may represent an alkyl group;

R^7 represents H, OH, protected hydroxy or O-alkyl, or in conjunction with R^1 it may represent =O;

R^8 represents H or OH;

R^{10} represents H, alkyl, alkyl substituted by one or more hydroxyl groups, alkenyl, alkenyl substituted by one or more hydroxyl groups, or alkyl substituted by =O;

Y represents O, (H,OH), (H,H), N-$NR^{11}R^{12}$ or N-OR^{13};

R^{11} and R^{12} independently represent H, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} independently represent H or alkyl;

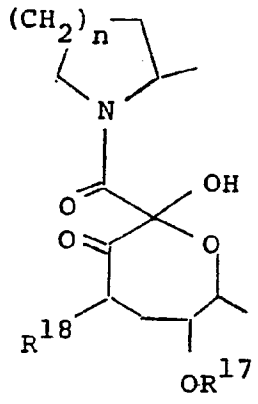
R^{20} and R^{21} independently represent O, or they may independently represent ($R^{20}a$,H) and ($R^{21}a$,H) respectively;

$R^{20}a$ and $R^{21}a$ independently represent OH, O-alkyl or $OCH_2OCH_2CH_2OCH_3$ or $R^{21}a$ represents protected hydroxy;

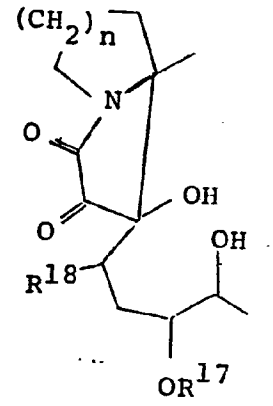
in addition, $R^{20}a$ and $R^{21}a$ may together represent an oxygen atom in an epoxide ring;

n is 1, 2 or 3;

X represents a group of the formula :

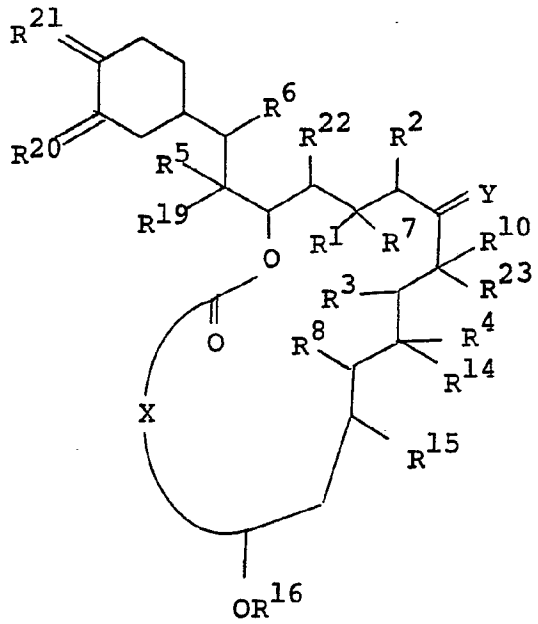


or a group of the formula :



in addition to their significances above, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a 5- or 6- membered N-, S- or O- containing heterocyclic ring, which may be saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl, hydroxy, alkyl substituted by one or more hydroxyl groups, O-alkyl, benzyl and $-CH_2Se(C_6H_5)$; and salts thereof.

2. A process for preparing a compound of the formula :



wherein each vicinal pair of substituents [R^1 and R^2], [R^3 and R^4], [R^5 and R^6] independently

a) represent two vicinal hydrogen atoms, or

b) form a second bond between the vicinal carbon atoms to which they are attached;

in addition to its significance above, R^2 may represent an alkyl group;

R^7 represents H, OH, protected hydroxy or O-alkyl, or in conjunction with R^1 it may represent =O;

R^8 and R^9 independently represent H or OH;

R^{10} represents H, alkyl, alkyl substituted by one or more hydroxyl groups, alkenyl, alkenyl substituted by one or more hydroxyl groups, or alkyl substituted by =O;

Y represents O, (H,OH), (H,H), N-$NR^{11}R^{12}$ or N-OR^{13};

R^{11} and R^{12} independently represent H, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} independently represent H or alkyl;

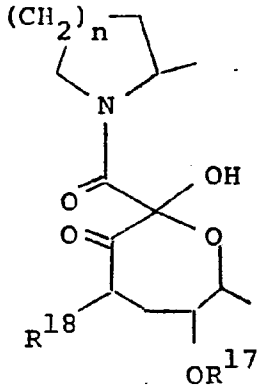
R^{20} and R^{21} independently represent O, or they may independently represent (R^{20}a,H) and (R^{21}a,H) respectively;

R^{20}a and R^{21}a independently represent OH, O-alkyl or $OCH_2OCH_2CH_2OCH_3$ or R^{21}a represents protected hydroxy;

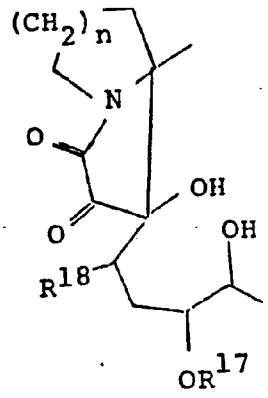
in addition, R^{20}a and R^{21}a may together represent an oxygen atom in an epoxide ring;

n is 1, 2 or 3;

X represents a group of the formula :

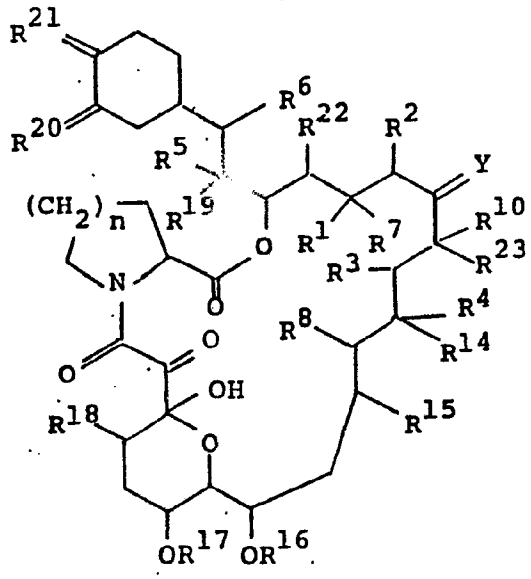


or a group of the formula :



in addition to their significances above, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a 5- or 6- membered N-, S- or O- containing heterocyclic ring, which may be saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl, hydroxy, alkyl substituted by one or more hydroxyl groups, O-alkyl, benzyl and $-CH_2Se(C_6H_5)$; or a salt thereof,

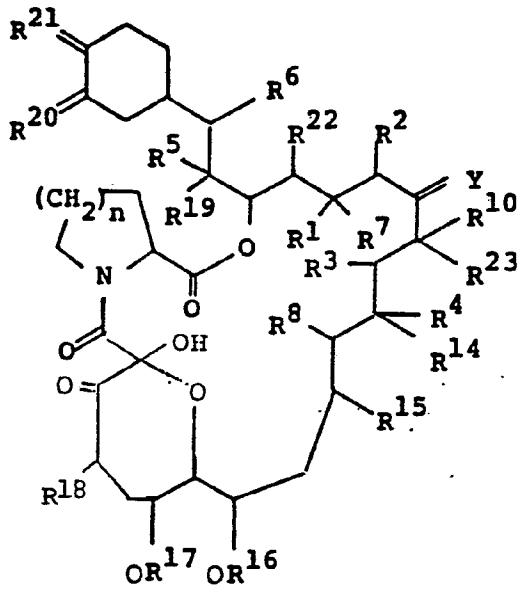
which comprises subjecting a compound of the formula:



wherein R^1 to R^8, R^{10}, R^{14} to R^{23}, Y and n are each as defined above,

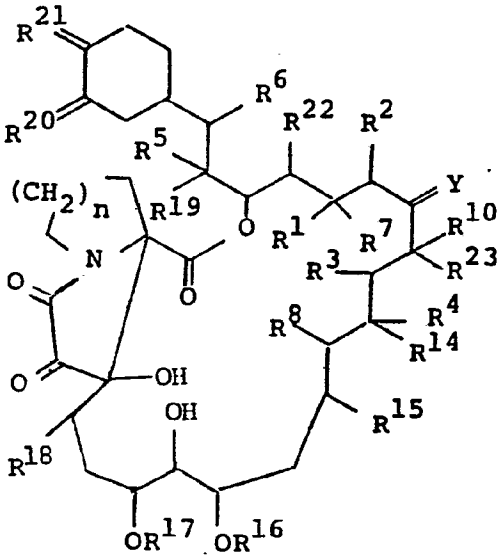
or a salt thereof, to rearrangement,

to give a compound of the formula :



of a salt thereof

and a compound of the formula :



or a salt thereof

wherein R^1 to R^8, R^{10}, R^{14} to R^{23}, Y and n are each as defined above.

3. A pharmaceutical composition containing tricyclo compounds of claim 1, as active ingredients, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

4. A use of tricyclo compounds of claim 1 as a medicament.

5. A method for treating or preventing resistance to transplantation, graft-versus-host diseases by medulla ossium, autoimmune diseases and infectious diseases which comprises administering a compound of claim 1 to human or animal.

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